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KLARQUIST SPARKMAN, LLP
121 S.W. SALMON STREET
SUITE #1600
PORTLAND, OR 97204-2988

EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,580	KASHMIRI ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8,10-12,16,20-28,32-35,44,45,47,48,52 and 67-89* is/are pending in the application.

4a) Of the above claim(s) *21,22,32-35,44,45,47,48,76-79 and 86-89* is/are withdrawn from consideration.

5)☒ Claim(s) *20* is/are allowed.

6)☒ Claim(s) *1-4,6,8,10-12,16,23-28,52,67-75 and 80-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Examiner in charge of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to the undersigned.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 28 May 2008 has been entered.

3. Claims 5, 7, 9, 13-15, 17-19, 29-31, 36-43, 46, 49-51 and 53-66 are cancelled.
Claims 1, 20 and 23 have been amended.
Claims 68-89 have been added.

4. Claims 21, 22, 32-35, 44-45, 47-48 and newly added claims 76-79 and 86-89 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

5. Claims 1-4, 6, 8, 10-12, 16, 20, 23-28, 52, 67-75 and 80-85 are under consideration.

6. This Office Action contains New Grounds of Rejections.

Rejections Withdrawn

7. The rejection of claim 56 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of “HuCC49V10” as the sole means of identifying the antibody is withdrawn in view of the cancellation of the claim.

8. The rejection of claims 1, 20, 23, 56 and 67 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological

materials are (1) known and readily available to the public; (2) reproducible from the written description is withdrawn in view of applicants' completion of the deposit requirements.

9. The rejection of claims 56 and 67 under 35 U.S.C. 112, first paragraph, because the specification, specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims is withdrawn in view of the cancellation of claim 56 and upon further consideration of claim 67.

Rejections Maintained

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. The rejection of claims 1-4, 6, 8, 10-12, 16, 23-28, 52 and now applied to newly added claims 68 and 80 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a humanized CC49 antibody, comprising: a light chain complementarity determining region (L-CDR)1, a L-CDR2, and a L-CDR3, a heavy chain complementarity determining region (H-CDR)1, a H-CDR2, and a H-CDR3, wherein a L-CDR3 of the humanized CC49 antibody or of the antigen binding fragment of the humanized CC49 antibody comprises a non-conservative amino acid substitution at position 91, wherein the tyrosine at position 91 is substituted with proline (HuCC49V10-14), and wherein the humanized CC49 antibody has a high binding affinity for TAG-72, compared to a parent CC49 antibody, wherein all the CDRs are from a parent human CC49 antibody, wherein the parent antibody is HuCC49V10 AND a humanized CC49 antibody, comprising: all four variable light chain framework regions and all four variable heavy chain framework regions of a human antibody; a light chain

complementarity determining region (L-CDR)1, a L-CDR2, a L-CDR3, a heavy chain complementarity determining region (H-CDR)1, a H-CDR2, and a H-CDR3, wherein at least one complementarity determining region (CDR) is a human antibody CDR and remaining CDRs are murine CC49 antibody CDRs; a non-conservative substitution of at position 91 in the L-CDR3 of the antibody, wherein the tyrosine at position 91 is substituted with proline; and a second substitution at position 27b of L-CDR1, wherein the valine at position 27b is substituted with leucine (HuCC49V10-15), wherein the humanized CC49 antibody has a high binding affinity for TAG-72, compared to a parent CC49 antibody, wherein the parent antibody is HuCC49V10, does not reasonably provide enablement for a humanized CC49 antibody, comprising: a light chain complementarity determining region (L-CDR)1, a L-CDR2, and a L-CDR3, a heavy chain complementarity determining region (H-CDR)1, a H-CDR2, and a H-CDR3, wherein a L-CDR3 of the humanized CC49 antibody or of any functional fragment of the humanized CC49 antibody comprises a non-conservative amino acid substitution at any position OR at any tyrosine residue of L-CDR3 OR substituting the tyrosine residue at position 91 with any amino acid, and wherein the humanized CC49 antibody has a high binding affinity for TAG-72, compared to a parent CC49 antibody OR a humanized CC49 antibody, comprising: a variable light framework region and a variable heavy framework region of a human antibody; a light chain complementarity determining region (L-CDR)1, a L-CDR2, a L-CDR3, a heavy chain complementarity determining region (H-CDR)1, a H-CDR2, and a H-CDR3, wherein at least one complementarity determining region (CDR) is a human antibody CDR and remaining CDRs are murine CC49 antibody CDRs; a non-conservative substitution of any residue is in the L-CDR3 of the antibody; and a substitution of any residue in any L-CDR or H-CDR of the antibody; wherein the humanized CC49 antibody has a high binding affinity for TAG-72 and is minimally immunogenic, compared to a parent CC49 antibody is maintained.

The above rejection has been withdrawn as it pertains to any functional fragment of the humanized CC49 antibody and “a variable light framework region and a variable heavy framework region of a human antibody” (e.g., claim 23) in view of the amendments to the claims and applicants’ arguments.

The rejection is maintained as it pertains to the claimed humanized CC49 antibody and antigen-binding fragments thereof (e.g., HuCC49V10) comprising a non-conservative amino acid substitution at any position OR at any tyrosine residue of L-CDR3 OR substituting the tyrosine residue at position 91 with any amino acid, and wherein the humanized CC49 antibody has a high binding affinity for TAG-72, compared to a parent CC49 antibody, or a humanized CC49 antibody (e.g., HuCC49V10) comprising CDRs and human framework regions, wherein at least one CDR is a human antibody CDR and remaining CDRs are murine CC49 antibody CDRs and wherein the humanized CC49 antibody comprises a non-conservative substitution at any residue is in the L-CDR3 and a substitution at any residue in any L-CDR or H-CDR of the antibody; wherein the humanized CC49 antibody has a high binding affinity for TAG-72 and is minimally immunogenic, compared to a parent CC49 antibody.

Applicants' arguments have been fully considered but are not persuasive. Applicants argue that a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction the experimentation should proceed. Applicant states that the CC49 and HuCC49V10 antibodies are described in the instant application and were well known at the time of filing. Further, applicant points out that the specification teaches and provides working examples (e.g., see citations at pg, 15 of the reply filed 5/28/08). Applicant concludes that based on the teachings in the specification and the knowledge of the skilled artisan, it would be simply a matter of routine experimentation to make the humanized CC49 antibodies having the claimed genus of residue substitutions and to test these antibodies for their binding affinity and immunogenicity. This is not persuasive because the teachings, guidance and exemplification in the specification are limited to two mutants of HuCC49V10, e.g., HuCC49V14 and HuCC49V15, which showed significantly higher antigen binding affinity and lower sera reactivity compared to the parental HuCC49V10 antibody. The specification discloses that the dissociation rates of only 6 isolated were lower than that of the parent antibody (HuCC49V10) as shown in Table 5 (Page 44, in particular) and the ELISA results show that the antigen-binding activity of only the two variants, HuCC49V10-14 and HuCC49V10-15, were

either comparable to or exceeded that of the parental HuCC49V10 (page 47, in particular). Further, in Table 5, the relative affinity binding of CC49 antibodies show that only HuCC49V10-14 and HuCC49V10-15 exhibited a better/high binding activity compared to the parent HuCC49V10; and the Flow cytometric analysis, in figure 6, showed that only two variants, HuCC49V10-14 and HuCC49V10-15 show significantly better binding to the cells displaying TAG-72 on their surface (page 50, in particular). In addition, the studies in regard to the sera reactivity of HuCC49V10 variants indicated that only HuCC49V10-14 and HuCC49V10-15 showed not only significantly higher antigen binding affinity that that of HuCC49V10, but they also showed much lower reactivity to sera from patients who showed an anti-idiotypic response to the parental CC49 antibody (page 53, in particular). The specification does not disclose the genus of CC49 antibody variants wherein the L-CDR3 comprises just any a non-conservative amino acid substitution, or just any tyrosine to proline substitution, or just any substitution at position 91, and optionally further comprising a substitution of a second residue in any heavy or light chain CDR, wherein the resulting CC49 variant has high binding affinity an minimal immunogenicity compared to the parental HuCC49V10. Thus, the teachings guidance and exemplification provided in the specification is limited relative to the broad scope of the claims art issue. Applicant's description as well as the cited art of Tamura et al, PCT/US89/04402 and PCT/US99/25552, without more precise guidelines, amount to little more than "a starting point, a direction for further research." *Genentech*, 108 F.3d at 1366. *See also Calgene*, 188 F.3d at 1374 ("the teachings set forth in the specification provide no more than a 'plan' or 'invitation' for those of skill in the art to experiment practicing [the claimed invention]; they do not provide sufficient guidance or specificity as to how to execute that plan"); *National Recovery Technologies*, 166 F.3d at 1198 (stating that patent-in-suit "recognizes a specific need… and suggests a theoretical answer to that need. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement"). The instant specification does not describe the claimed invention in terms that will "enable any person skilled in the art… to make and use" the invention commensurate in scope with the claims. At

most, the specification will enable a person of ordinary skill in the art to attempt to discover how to practice the claimed invention.

The specification does not enable the genus and various subgenera because where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one particular species, what other species will work. See MPEP 2164.03. As cited in the previous Office Action the art also points out that changing the complementary determining regions is a hit and miss proposition and even minor changes in the amino acid sequences of heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidence by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79:1979-1983, 1982; cited on PTO-892 mailed 12/28/07) and Colman P. M. (Research in Immunology, 145:33-36, 1994, cited on PTO-892 mailed 12/28/07). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma antibody resulted in the loss of antigen-binding function. Colman P. M. teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column). Finally, it was well established in the art that the CDRs have a particular order, particular length and that the formation of an intact antigen-binding site of most antibodies routinely requires the association of the complete heavy and light chain variable regions of an antibody each of which consists of three CDRs or hypervariable regions presented in a specific order, which provide the majority of the contact residues for the binding of the antibody to its target epitope Paul ed. Fundamental Immunology, 3rd Edition, 1993, pp 292-295, PTO-892 mailed 7/20/06). While many changes are theoretically possible, the art does not recognize

predictable substitutions of individual CDR amino acids that bind the same antigen, or have the binding characteristics as broadly embraced by the claims. The issue remains the description of the claimed antibody variants and guidance and direction of the specification for the claimed variants.

Additionally, the language of claim 23 and claims depending therefrom broadly embraces humanized CC49 antibodies that comprise one, two, three, four or five human CDRs in combination with as few as one CC49 CDR, i.e., "at least one CDR is a human antibody CDR..." is open claim language that is inclusive to up to five human CDRs in the humanized CC49 antibody. While applicant has demonstrated that HuCC49V10 comprising the L-CDR1 and L-CDR2 regions from the human LEN antibody, wherein the huCC49V10 retains the antigen specificity of the parental CC49 antibody (TAG-72), applicant has not demonstrated that humanized CC49 antibodies comprising just any human L-CDR1 and L-CDR2 or comprising only one, two or three CC49 CDRs would maintain the binding characteristics of the parental CC49 antibody. Thos of skill in the art recognize that "humanizing" antibodies involves the substitution of all six CDRs from a rodent antibody that binds an antigen of interest, and that all six CDRs are involved in antigen binding (see entire document, but especially Figures 1-3). Similarly, the skilled artisan recognized a "chimeric" antibody to be an antibody in which both the heavy chain variable region (which comprises the three heavy chain CDRs) and the light chain variable region (which comprises the three light chain CDRs) of a rodent antibody are recombined with constant region sequences from a human antibody of a desired isotype (e.g., Bendig M. M. (Methods: A Companion to Methods in Enzymology, 1995; 8:83-93; cited on PTO-892 mailed 12/28/07; see Figures 1-3). Thus, the state of the art recognized that it would be highly unpredictable that a humanized antibody comprising less than all six CDRs of a parental antibody with a desired specificity would retain the antigen-binding function of the parental antibody. Thus, the minimal structure which the skilled artisan would consider predictive of the function of binding antigen includes six CDRs (three from the heavy chain variable region and three from the light chain variable region) from the same parental antibody in the context of framework sequences which maintain their correct spatial orientation

have the requisite antigen-binding function. Therefore, one of skill in the art could not predictably extrapolate the teachings in the specification limited to HuCC49V10 comprising murine CC49 CDRs except that L-CDR1 and L-CDR2 are replaced with the corresponding human LEN L-CDR1 and L-CDR2 regions wherein HuCC49V10 retains the TAG-72 specificity and wherein two variants of HuCC49V10, V14 and V15, further comprise a tyrosine to proline substitution at Kabat position 91 in L-CDR3 (V14) and further comprise the tyrosine to proline substitution at Kabat position 91 in L-CDR3 and a valine to leucine substitution at Kabat position 27b in L-CDR1 (V15), which retain the TAG-72 antigen specificity to humanized CC49 antibodies comprising just any human L-CDR1 and L-CDR2 or comprising only one, two or three CC49 CDRs would maintain the binding characteristics of the parental CC49 antibody.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul W. E., Rudikoff et al and Bendig M. M., (all of record) the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed antibody variants that retain the parental TAG-72 specificity for the treatment of cancer, with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed humanized antibodies and absent working examples providing evidence which is reasonably predictive that the claimed humanized antibody variants bind TAG-72, commensurate in scope with the claimed invention.

New Grounds of Objections/Rejections

12. Claims 80 and 83 are objected to in the recitation "H-CDR3of", which should be corrected to "H-CDR3 of".

Appropriate correction is required.

13. Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Claim 6 recites wherein the L-CDR1 and L-CDR2 are a human antibody L-CDR1 and L-CDR2, whereas base claim 1 recites that all of the heavy and light chain CDRs are of a parent antibody wherein the parent antibody is HuCC49V10. The specification discloses that HuCC49V10 is a humanized CC49 antibody comprising murine CC49 CDRs except that L-CDR1 and L-CDR2 are replaced with the corresponding human LEN L-CDR1 and L-CDR2 regions. Thus, base claim 1 is directed to humanized CC49 antibodies that comprise human LEN L-CDR1 and L-CDR2 regions and thus, claim 6 which recites that L-CDR1 and L-CDR2 may be any human L-CDR1 and L-CDR2 does not incorporate all of the limitations of the base claim and further add a limitation. Applicant is reminded that the fourth paragraph of 35 U.S.C. 112, states that "a claim in a dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers" and requires the dependent claim to further limit the subject matter claimed.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 23-28, 67-75 and 80-85 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 23-28, 67-75 and 80-85 are vague and indefinite in the recitation of "HuCC49V10" in claims 23, 67-68, 70, 80 and 82 as the sole means of identifying the parent antibody. The use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same

laboratory designations to define completely distinct molecules. This rejection can be obviated by amending the claims to specifically and uniquely identify, for example, by SEQ ID number or by biological deposit accession number, e.g., see claim 1.

16. Claim 20 is free of the prior art and in condition for allowance.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For

more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643